DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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November 3, 2004

Donald E. Wilson, M.D., M.A.
Dean, School of Medicine
University of Maryland Baltimore Professional Schools
655 West Baltimore Street
Baltimore, MD 21201-1559

RE: Human Research Subject Protections Under Federalwide Assurance FWA-7 145

Research Project: A Phase II Randomized Trial Comparing Iodine-125 Versus Palladium-103 for Low Risk Prostate Cancer
Principal Investigator: Dr. Steven DiBiase
Project Number: GCC 0002

Dear Dr. Wilson:

The Office for Human Research Protections (OHRP) has reviewed the University of Maryland Baltimore Professional School's (UMB) April 28, 2004 report responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) OHRP finds that the informed consent documents reviewed and approved by the UMB institutional review board (IRB) for this research failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): The expected duration of the subject's participation.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. In specific, the following risks and discomforts were not described: urinary frequency, urinary urgency, urinary hesitancy, dysuria, and rectal irritation. In addition, the risks of the alternatives were expressed in percentages, but the risks of the research procedures were not quantified at all, which made it

difficult to compare the research to the alternatives.

In addition, an incorrect and incomplete version of the informed consent document was approved by the UMB IRB when a modification was submitted. This error was not caught by the IRB until OHRP's investigation; however, OHRP acknowledges UMB's statement that the incorrect version was never used to obtain informed consent from any subject.

Corrective Action: OHRP acknowledges UMB's statement that the UMB IRB has been restructured over the past year, and that the IRB coordinators now conduct administrative review of all submissions to assure that the submission is complete and that the informed consent document accurately reflects the protocol and incorporates all elements required by HHS regulations. In addition, the UMB IRB's new electronic document management system allows coordinators to compare an amended protocol or informed consent document to the previously approved version, and continuing education of investigators and research staff regarding good clinical practices is ongoing. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the UMB assurance.

(2) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB chair or another IRB member designated by the chair, continuing review must occur no more than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds the IRB failed to conduct continuing review of this research at least once per year, and that brachytherapy of one subject was conducted during this lapse in approval.

OHRP acknowledges UMB's statement, "However, the only part of the study that was considered 'research' as opposed to standard care was the randomization to either I-125 or Pd-103 seeds." However, OHRP notes that the brachytherapy procedures were dictated by the protocol, and that the protocol also included data collection for research purposes; and that, therefore, the brachytherapy and data collection were all part of the research.

The IRB and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB, or if the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.

Corrective Action: OHRP acknowledges that the UMB IRB's new electronic document management system, as well as ongoing continuing education of investigators and research staff regarding good clinical practices, should prevent lapses of IRB approval of protocols. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the UMB assurance.

OHRP has the following additional questions about the above-referenced research:

(3) [Redacted]

OHRP makes the following determinations regarding general human subjects protections at UMB:

(4) OHRP finds that UMB IRB members were not advised of (a) research protocols approved at the time of initial or continuing review under an expedited review procedure, or (b) minor changes in research protocols approved under an expedited review procedure, as required by HHS regulations at 45 CFR 46.110(c).

Required Action: By December 15, 2004, please provide OHRP with a corrective action plan to address this determination.

(5) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the *Federal Register* at 63 FR 60364-60367. OHRP finds that the UMB IRB inappropriately applied expedited review to continuing review of research that involved greater than minimal risk and does not appear in the categories of research published in the *Federal Register*.

Corrective Action: OHRP acknowledges UMB's statement that continuing review of greater than minimal risk studies by the convened IRB was implemented in August 2001; however, the copies of the minutes of IRB meetings at which this procedure was supposedly implemented do not mention this. By December 15, 2004, please provide OHRP with written procedures which implement this important change.

(6) OHRP finds that the institution does not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for conducting its continuing review of research.

(b) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(c) The procedures which the IRB will follow for determining which projects require review more often than annually.

(d) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(e) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(f) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Required Action: By December 15, 2004, please provide OHRP with a corrective action plan to address this determination. OHRP acknowledges UMB's statement in your April

28, 2004 report that the IRB was in the process of developing new written procedures. Please provide OHRP with a copy of any procedures that have been developed since that date.

OHRP has the following additional guidance:

(1) In section V.8 of the University of Maryland School of Medicine IRB Policies and Procedures Manual, an outdated link to OPRR exists. In addition, the University of Maryland IRB Policies and Procedures Manual includes an outdated link to the OHRP homepage. Please update both to OHRP's current home page address: http://www.dhhs.gov/ohrp/.

(2) Section VII of the University of Maryland School of Medicine IRB Policies and Procedures Manual states that "the federal regulations governing [research involving pregnant women and fetuses] is currently under revision." Section III.C of the University of Maryland School of Medicine IRB Policies and Procedures Manual states the same thing. The Criteria for IRB Approval of Reserach and Documentation for Research Involving Vulnerable Populations, Research IRB Checklist includes references to the old 45 CFR part 46, subpart B. Please note that the regulations at 45 CFR part 46, subpart B (Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research) have been revised.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc: Ms. Susan Buskirk, Program Manager, Human Research Protections, UMB
Dr. Robert Edelman, Chair, UMB IRBs
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
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Ms. Shirley Hicks, OHRP
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